

**SUMMARY OF EXPERT COMMENTS FOR THE
NATIONAL ACADEMY OF SCIENCES (NAS) COMMITTEE
TO ASSESS THE HEALTH IMPLICATIONS OF PERCHLORATE INGESTION**

Submitted by:

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EXECUTIVE SUMMARY

This document provides a summary of expert comments submitted by the Perchlorate Study Group (PSG) for the National Academy of Sciences (NAS) Committee to Assess the Health Implications of Perchlorate Ingestion. This document is organized to follow the detailed, interagency consensus Charge provided by the White House Office of Science and Technology Policy (OSTP). Simply, key points the Committee should consider in response to each Charge question are summarized with references provided, as available, to support more detailed inquiry by the Committee as they deem necessary.

The PSG has funded several highly qualified experts to develop the best, most scientifically defensible understanding of perchlorate and its potential to cause adverse effects. We provided extensive and detailed analysis and comments to U.S. EPA regarding their 2002 External Review Draft (U.S. EPA 2002) risk assessment (“ERD”) during the comment period in 2002. To this date, 19 months since the last U.S. EPA peer review, we have heard no response to our comments. This document briefly summarizes our original comments to U.S. EPA (PSG 2002), as well as additional analysis done more recently, and our general areas of agreement or disagreement with the ERD. Cited reports are included on the CD that is being provided concurrently with copies of this report. The document ends with considerations important to the Committee’s development of an informed response to the Charge.

We understand that review of public comments received by U.S. EPA is one of the essential elements of the Committee’s charge. An overview of our comments is summarized below.



The state of the science of perchlorate is rich, comprehensive, and detailed for humans and for animals—especially when compared with other environmental contaminants. Studies relating to perchlorate pharmacology, toxicology, endocrinology, reproduction, cancer, mutagenesis, immunology, epidemiology, occupational health, and pharmacokinetics have been conducted.

Perchlorate is one of the best-studied environmental chemicals from both a pharmacological and toxicological perspective. The perchlorate database is robust, not uncertain. For instance:

- The pharmacokinetics and the pharmacodynamics of perchlorate are well-characterized in humans and lab animals.
- Since 1997, at least 13 new toxicological studies have been conducted in animals, including subchronic studies, developmental studies in two species, a multigeneration reproductive study, a rodent cancer study, and mutagenicity studies. None of these studies shows a bona fide adverse effect at the doses administered.
- Also since 1997, two well-designed and controlled human clinical studies have been performed to characterize the threshold of perchlorate’s mechanism of action—the inhibition of iodide uptake. Both found no adverse effects or changes in thyroid hormones and blood chemistry that would demonstrate even the earliest onset of hypothyroidism at any dose tested. Both were able to identify a no-observed effect level (NOEL) and estimate a no-effect level (NEL). These studies establish the lower bound for any scientifically valid level of exposure that is without appreciable risk to human health, including the health of sensitive subpopulations.

- In addition, two occupational studies in humans demonstrate that exposure over several years at levels hundreds of times greater than the threshold for inhibition of iodide uptake also causes no adverse effects or changes in thyroid hormones and blood chemistry. These results support the conclusion that exposures at the NOEL or NEL are highly protective.
- Adding to the database, several ecological epidemiological studies of people in the U.S. suspected to be exposed to low concentrations of perchlorate in drinking water, or known to be exposed to levels, as high as 100 ppb in one study, have found no effects on blood chemistry, thyroid hormones, or TSH.

U.S. EPA has proposed a conceptual model that is at best, only partially acceptable. Their model (Figure 3-12, ERD 2002) implicitly defines as “adverse” a precursor (inhibition of iodide uptake) of a precursor (transient changes in thyroid and pituitary hormones or thyroid hypertrophy) of a precursor (sustained and substantial changes in thyroid hormones or thyroid hyperplasia) of an adverse effect (fetal CNS effects). Inhibition of iodide uptake is a biochemical phenomenon that is mundane, commonplace, and reversible. Establishing a “safe” exposure level based on its threshold would be overly protective. Furthermore, applying a large composite uncertainty factor on top of this constitutes duplicative layers of precaution and would be a radical departure from historic risk assessment practice.

Not only is inhibition of iodide uptake not adverse, U.S. EPA also assumes a disease model in which a hypothetical transient change in thyroid hormones is adverse. Figure 7-2 in the ERD shows schematically that the Agency assumes that any change in hormones defines “clinical disease,” and their model does not allow for a normal variation of thyroid hormones (*i.e.*, homeostasis).

Therefore, U.S. EPA’s proposed model is only acceptable as a generic and simplistic representation. In certain areas the model is oversimplified to the point where it invites erroneous inferences when juxtaposed with well-known fundamentals of thyroid endocrinology. These errors must be fixed before the model can be used for human health risk assessment.

A more realistic model would take into account fundamental biochemical and physiological phenomena. The correct model recognizes that fluctuations in triiodothyronine (T_3), T_4 , and TSH are normal, adaptive phenomena and should not be construed as adverse (Delange 2000). Iodide uptake by cells is a common and redundant biochemical event. In fact, many chemicals in the foods we eat inhibit iodide uptake or affect some other aspect of thyroid function. Physiological regulatory mechanisms protect against effects of moderate changes in iodide supply (Pisarev and Gartner 2000).

Clinical and epidemiological studies show that a considerable amount of perchlorate exposure can be sustained without hormone changes. Further, humans clearly possess a significant capability to adapt to marginally low iodine intake without adverse effects on thyroid hormone balance. In no case could inhibition of iodide uptake be construed as comparable to the effects of hormonal modification so substantial that they result in developmental changes.

A correct and realistic model addresses substantial and sustained changes in maternal thyroxine (T_4) as the sentinel precursor of neurodevelopmental injury. As described by Abbassi (2002):

Factors that may impair the adequacy of thyroxine production by the maternal thyroid are risk factors for the developing fetus. The two well-known factors that may lead to maternal hypothyroidism are autoimmune thyroiditis and severe iodine deficiency...Iodine deficiency is only a problem when it leads to hypothyroxinemia in the mother.

Inhibition of iodide uptake cannot be equated with these effects.

Based on the animal studies conducted, no reliable evidence exists of any adverse effect not mediated by inhibition of thyroidal iodide transport. The U.S. EPA analysis maintains that the animal developmental studies show effects of perchlorate on neurodevelopment at extremely low doses. Expert review and analysis of these studies has concluded that the studies do not support this conclusion.

For instance, U.S. EPA inappropriately concluded that there were exposure-related effects of perchlorate on neurobehavioral endpoints. However, U.S. EPA's interpretations of the studies' findings are contradicted by those of the study investigators. More recently, an expert review panel at the University of Nebraska concluded that the behavioral studies could not be interpreted as showing an effect of perchlorate.

U.S. EPA also interpreted positive effects from perchlorate on brain morphometry that were not found by the study authors. Comments submitted to U.S. EPA demonstrate that measurements were fatally flawed by methodological deficiencies and were not interpretable. The expert review panel at the University of Nebraska also concluded that the brain morphometry data could not be used.

U.S. EPA also concludes that the rat data found thyroid tumors in a 19-week study, and that these tumors are relevant to human risk assessment. The rat study was not a valid study of carcinogenicity. Other U.S. EPA work has concluded that the rat is not an appropriate model of thyroid tumors in humans.

Even at the highest dose tested, the animal studies do not demonstrate reliable evidence of any adverse effect. This is a critical point. We contend that the animal data used by U.S. EPA show no reliable evidence of the assumed adverse effects of perchlorate, and only flawed reasoning and analysis supports the finding of neurodevelopmental or neoplastic effects.

U.S. EPA fails to consistently consider and evaluate human studies. The ERD suggests that inhibition of iodide uptake is itself an adverse effect by arguing that any inhibition of iodide uptake could lead to thyroid hormonal changes. U.S. EPA proposes to set the level for "safe" exposure at 1 ppb.

U.S. EPA uses a subset of the data developed by the late Dr. Monte Greer and colleagues, but refused to examine the Greer *et al.* (2002) study. This study is an excellent clinical study and is consistent with previously published thyroid work. Based on Greer *et al.* (2002), the level of perchlorate exposure needed to cause 70% inhibition of iodide uptake is approximately 17,000 ppb in drinking water. No changes in thyroid hormones or blood chemistry were observed.

The leading occupational exposure study (Lamm *et al.* 1999) confirms that this dose yields no changes in thyroid hormones or blood chemistry despite years of exposure. The minimum level of perchlorate exposure needed to cause even transient changes in thyroid hormone levels is unknown, but there is substantial evidence that this threshold exceeds 17,000 ppb in drinking water.

U.S. EPA maintains that there are ecological epidemiology studies that suggest an effect of perchlorate at levels that currently exist in drinking water in the U.S. The findings of both of those studies have been rejected by subsequently published analysis. The Agency relies on one published paper (Brehner *et al.*, 2000) and an unpublished thesis (Schwartz 2001). Further published analysis of the published data (Lamm 2003b) shows that the observed effect represented a regional difference as and not an exposure effect (there was no difference from unexposed neighboring communities). In addition, an improvement on the unpublished study that is in press found no effect (Kelsh 2003). Long-term epidemiological studies demonstrate that exposures exceeding 100 ppb in drinking water do not affect thyroid hormone levels in children receiving adequate iodine nutrition. The level of perchlorate exposure that is without any detectable effect in humans is approximately 200 ppb perchlorate in drinking water—10 to 40 times greater than environmentally relevant exposure levels in the U.S. Contrary to U.S. EPA's conclusion, there is no epidemiological proof, or any suggestion of support for a health effect of existing perchlorate levels.

U.S. EPA suggests that hypothyroidism makes people more susceptible to perchlorate exposure. However, in the U.S., hypothyroidism is caused mainly by autoimmune disease and other disease states that are not related to iodine supply. If iodine is not a limiting factor in any existing disease state, then pregnant women exposed to environmentally relevant doses of perchlorate are not susceptible to hypothyroxinemia and hypothyroidism due to perchlorate. This is principally because environmental exposure levels are an extremely small fraction of the amount necessary to cause any decline in thyroid hormones, much less the substantial and sustained decline that would be a precursor to fetal CNS effects. Babies born to women who are (or who may become) hypothyroid due to iodine deficiency are the most plausible subpopulation of concern, but even this group should be fully protected as long as chronic perchlorate exposure stays below 200 ppb in drinking water.

Use of human studies in the risk assessment process is important to the assignment of uncertainty factors used to approximate a safe lifetime exposure for humans, including sensitive subpopulations. Adequate human data eliminates the need to rely on rat data. Further, data from studies in humans are clearly preferred when they are available and more so when the underlying rat studies have substantial methodological problems.

In summary, U.S. EPA has made the exceptionally well-characterized and understood science of perchlorate unnecessarily confusing and complex.

Thus, rather than the strong case for a link between perchlorate levels that cause minimal inhibition of iodide uptake and these adverse effects, we believe the only reliable connection between perchlorate and the putative adverse effect is the conceptual model that connects the two, and the known effects of severe iodine deficiency. U.S. EPA collapses the model by finding all of these effects in a data set when the effects are not there and by failing to appropriately consider valid data to the contrary.

These comments are submitted on behalf of the Perchlorate Study Group (PSG) to the National Academy of Sciences (NAS) Committee to Assess the Health Implications of Perchlorate Ingestion. Our review follows the interagency consensus Charge provided by the White House Office of Science and Technology Policy (OSTP) and offers answers to each of the scientific questions posed by the Charge. Following our review is a discussion of additional considerations the NAS Committee may wish to review in their assessment.

The PSG has funded several highly qualified experts to develop the best, most scientifically defensible understanding of perchlorate and its potential to cause adverse effects. We provided extensive and detailed analysis and comments to U.S. EPA regarding their 2002 External Review Draft (U.S. EPA 2002) risk assessment (“ERD”) during the comment period in 2002. To this date, 19 months since the last U.S. EPA peer review, we have heard no response to our comments. This document briefly summarizes our original comments to U.S. EPA (PSG 2002), as well as additional analysis done more recently, and our general areas of agreement or disagreement with the ERD. Cited reports are included on the CD that is being provided concurrently with copies of this report. The document ends with considerations important to the Committee’s development of an informed response to the Charge.

1.0 RESPONSE TO CHARGE QUESTION I

1.1 What is the current state-of-the-science or understanding regarding the potential for adverse effects due to disruption of thyroid function in humans and other animals at various stages of life?

1.1.1 The state of the science of perchlorate is rich, comprehensive, and detailed for humans and for animals.

The state of the science of perchlorate is rich, comprehensive, and detailed—especially when compared with other environmental contaminants. Studies relating to perchlorate pharmacology, toxicology, endocrinology, reproduction, cancer, mutagenesis, immunology, epidemiology, occupational health, and pharmacokinetics have been conducted.

Environmentally relevant levels of perchlorate exposure (*e.g.*, <200 ppb in drinking water) pose no risk to healthy adults and children. Environmentally relevant levels of perchlorate exposure pose a theoretical hazard to the developing fetus via the pregnant woman, but only pregnant women who are hypothyroid due to iodine deficiency (see Section 2.1.1). Children born to such women face much greater risk from their mothers’ underlying iodine deficiency than they do from perchlorate (see Section 2.1.2). Fortunately, the available empirical evidence indicates that this sub-population is at most extremely small and may not in fact exist (see Section 1.4.1.1).

1.1.1.1 The pharmacological mechanism of action for perchlorate has been known for over 50 years.

Perchlorate has been known for over 50 years to interfere with the entry of iodine into the thyroid gland. Since early in the twentieth century, it has been known that the thyroid gland uptakes iodide to make thyroid hormone. Iodine is a natural element and a member of the Hofmeister series as a chemical family. In the early 1950s, Stanbury and Wyngaarden (1952) explored various members of this family to determine whether any of them might interfere with iodine's entry into the thyroid gland and thus slow down hyperactive thyroids in patients with Graves' disease. They determined that at daily doses of 100 mg per subject, perchlorate was particularly able to both reduce the iodide content of the thyroid gland and block the thyroid's uptake of iodide for about six hours after a dosage. Subsequently, the use of large doses of perchlorate, in some cases a gram or more per day, became a successful treatment for Graves' disease.

1.1.1.2 The toxicological database for perchlorate is extensive.

The pharmacokinetics and pharmacodynamics of perchlorate are well characterized in humans and lab animals. Since 1997, at least 13 new toxicological studies have been conducted in animals, including subchronic studies, developmental studies in two species, a multigeneration reproductive study, a rodent cancer study, and mutagenicity studies (see Appendix A). No effects were found in these standard developmental, reproductive, genotoxicity, or subchronic studies other than the thyroid effects that are secondary to inhibition of iodide uptake. More is known about perchlorate than perhaps any other environmental contaminant.

In his oral remarks at the first peer review of the 1998 U.S. EPA Draft Risk Assessment (see Appendix B), Dr. Curtis Klaassen, Chair of the peer review panel, commented on the depth of understanding of perchlorate's mechanism of action relative to other chemicals U.S. EPA regulates. He stated:

[W]e do not only know the mode of action, we know the exact molecule that it interacts with. Can you give me twelve other chemicals that we know exactly the molecular mechanism of action, with what the chemical... what the chemical interacts with to then produce toxicity? I don't know of any. I mean it is really amazing. That perchlorate up there in the left-hand corner interferes with the uptake of iodide. It interferes with that transporter... with that molecule. We know that. And all of the toxicity after that is due to that one chemical interaction.

Yet in 2002, U.S. EPA responded to this wealth of new scientific information by increasing the composite uncertainty factor for the draft perchlorate reference dose (RfD) from 100 in 1998 to 300 in 2002. A rising composite uncertainty factor is typically inconsistent with advancing scientific knowledge (see Section 4.1). Most disturbingly, the use of large composite uncertainty factors implies a rejection of negative scientific evidence in favor of policy-driven precaution.

1.1.1.3 All other things constant, human data should be preferred to animal data.

In its Proposed Guidelines for Carcinogenic Risk Assessment (U.S. EPA 1996), U.S. EPA states:

... when available human data are extensive and of good quality, they are generally preferable over animal data and should be given greater weight in hazard characterization and dose response assessment, although both are utilized.

U.S. EPA Risk Assessment Guidance for Superfund (U.S. EPA 1989) also emphasizes the preference for human data over animal data when identifying the critical study and determining the no observed adverse effect level (NOAEL) for development of oral RfDs. Specifically, this guidance states:

If adequate human data are available, this information is used as the basis of the RfD. Otherwise, animal study data are used; in these cases, a series of professional judgments are made that involve, among other considerations, an assessment of the relevance and scientific quality of the experimental studies.

Dr. Klaassen also highlights this point in the 1999 U.S. EPA Perchlorate Risk Assessment Peer Review Workshop Report (see [Appendix C](#)). He states:

Risk assessments that estimate human risk from data on human populations should be more accurate than ones that rely on animal data. This can be done with adequate occupational exposure studies or administration to humans with thyroid disease. With a chemical like perchlorate, which has been used as a drug, a NOEL can be established in humans. The therapeutic dose given to humans is approximately 10 mg/kg. Thus, 10 mg/kg is too high for environmental perchlorate exposure. Further studies on healthy human volunteers are encouraged, such as those being conducted at Harvard and in Germany, to establish exposures that will protect humans from potential adverse effects of perchlorate exposure (using as a biomarker a dose that does not increase TSH).

Noting the importance of conducting additional studies in order to have a scientific justification for increasing the RfD, Dr. Klaassen further states:

If the appropriate human data are accumulated, the uncertainty factor could be small. The magnitude of the uncertainty factor needs to wait until all the relevant studies are complete. Based on the lack of demonstrated adverse effects, the RfD proposed by the EPA (0.0009 mg/kg/day) is likely to be conservative. (see [Appendix C](#))

1.1.1.4 Rodents do not provide an appropriate model for estimating the effects of environmental chemicals on the human thyroid and should not be used for human health risk assessment.

Rats and humans share the same basic thyroidal mechanisms and regulatory systems, but the homeostatic responses of the two species are quite different ([Goodman 2003a](#)). Further support of these differences comes from [Greer et al. \(2002\)](#), which reports, "...although the physiology of the pituitary-thyroid axis is very similar in the rat and the human, the rat thyroid is much more rapidly responsive to any perturbation of iodine metabolism leading to decreased thyroid hormone formation." These species differences affect the validity of extrapolations to humans from observations in rats.

The weight of the evidence suggests that rodents are more sensitive than human subjects to thyroid tumor induction due to hormonal imbalances that cause elevated thyroid stimulating hormone (TSH) levels. At least 20 different compounds cause follicular cell neoplasms of the thyroid in rats and/or mice, but none is unequivocally associated with thyroid cancer in humans (Capen *et al.* 1999). When human patients have markedly altered thyroid function and elevated TSH levels, as in areas with high incidence of endemic goiter due to iodine deficiency, there is little if any increase in the incidence of thyroid cancer. The relative resistance to the development of thyroid cancer in humans with elevated plasma TSH is in marked contrast to the response of the thyroid gland to chronic TSH stimulation in rats and mice (Capen 1992 and 1994).

Epidemiologic studies of exposure to thiocyanate, another anti-thyroid agent present in the diet, also fail to demonstrate an increase in thyroid cancer. They indicate a protective effect from inhibition of iodide uptake in iodine sufficient populations (see Appendix D).

1.2 Does the state-of-the-science support U.S. EPA's proposed model of potential adverse effects of perchlorate resulting from inhibition of iodide uptake?

1.2.1 U.S. EPA's proposed conceptual model is acceptable only as a generic and simplistic model.

U.S. EPA's model correctly recognizes that the pharmacological effect of large doses of perchlorate is to competitively suppress iodide uptake by the sodium-iodide symporter (NIS), the passageway for iodide ion into the thyroid gland. This pharmacologic knowledge has been known for more than 50 years. However, U.S. EPA's proposed model implicitly defines as "adverse" a precursor (inhibition of iodide uptake) of a precursor (transient changes in thyroid and pituitary hormones or thyroid hypertrophy) of a precursor (sustained and substantial changes in thyroid hormones or thyroid hyperplasia) of an adverse effect (fetal CNS effects). Inhibition of iodide uptake is mundane, commonplace, and reversible, and should not be construed as necessarily adverse.

While reasonably representing the qualitative relationships between the sequential effects, the U.S. EPA schematic representation and text descriptions fail to consider the quantitative relationships between:

- Perchlorate dose and extent of inhibition of iodide uptake;
- Inhibition of iodide uptake and extent of thyroid hormone changes; or
- Thyroid hormone changes and extent of neurodevelopmental effect.

U.S. EPA collapses all of these effects, leading to their prediction that any degree of inhibition of iodide uptake could be associated with adverse neurodevelopmental effects. This is a gross oversimplification of the conceptual model.

Furthermore, the model incorrectly includes "tumors" as a consequence of perchlorate exposure. According to FDA's National Center for Toxicological Research, "There is no evidence for a primary causative role of TSH in thyroid tumor formation in humans..." (Poirier *et al.* 1999). Scientific evidence supports the conclusion that perchlorate does not cause cancer in humans (see Appendix D).

1.2.1.1 U.S. EPA's interpretation of the conceptual model errs in a number of ways.

The proposed model lacks a clear definition of what is an adverse effect. The model errs by implicitly identifying inhibition of iodide uptake as an adverse effect, the prevention of which then becomes essential to prevent neurodevelopmental injury. Inhibition of iodide uptake is the mechanism of action of perchlorate, not an adverse effect.

The mode of action model interprets any change in circulating thyroid hormone levels or TSH as adverse. It is widely agreed that neurodevelopmental injury cannot occur apart from these effects, but mere perturbations in thyroid hormone levels cannot by themselves impart any such injury. Changes in circulating thyroid hormone levels are normal aspects of homeostasis. To call a normal phenomenon "adverse" is to drain the word of meaning.

Severity is missing from the model. The mode of action model ignores the inherent reversibility of each progressive step along the pathway from exposure to genuine adverse effect. Unless they are severe, effects that are reversible typically are not interpreted as adverse. It is a radical departure from traditional risk assessment practice to consider effects adverse that are both reversible and indistinguishable from natural fluctuations in the body.

Dose-response for each variable in the model is missing. U.S. EPA's model fails to acknowledge the quantitative difference between the threshold for inhibition of iodide uptake and the level at which perchlorate causes uncompensated changes in circulating thyroid hormones (Abbassi 2002; Goodman 2003a; Greer *et al.* 2002; Fisher 2002; Maberly 2002). This effect is consistent with the definition of hypothyroidism as a decrease in thyroxine (T₄), a condition known as hypothyroxinemia. As described by Goodman (2003a), "All potential health effects of perchlorate are related to the scenario in which inhibition of thyroidal uptake of iodide over a prolonged period (months to years) leads to hypothyroxinemia."

U.S. EPA presumes that all effects are adverse, and that no effects are adaptive even within normal limits. The mode of action model fails to distinguish normal fluctuations in TSH and T₄ (adaptive effects) from sustained and substantial decrements in T₄ that could result in neurodevelopmental injury (genuinely adverse effects). The Agency says that any perturbation at all of thyroid hormones is adverse.

U.S. EPA incorrectly presumes that effects that occur only in animals (e.g., cancer) also occur in humans. Perchlorate is not a direct carcinogen via genotoxicity. Perchlorate has been shown to cause thyroid neoplasia in rodents secondary to chemically induced hormone imbalance, which predominantly involves effects on thyroid hormone synthesis or peripheral hormone disposition (McClain 1995). Thyroid gland neoplasia, secondary to chemically induced hormone imbalance, is mediated by TSH in response to altered thyroid gland function (Capen 1992, 1994). Human exposure to perchlorate at levels that do not affect or disrupt thyroid function cannot pose an appreciable risk of causing thyroid neoplasia (see Appendix D).

By calling it a "key event," U.S. EPA incorrectly implies inhibition of iodide uptake is adverse. The traditional point of departure in toxicological risk assessment is the identification of the "critical effect." Both science and judgment are required to identify critical effects. Still, there has been a longstanding consensus that the critical effect should be the first genuinely adverse biological outcome. The Agency's mode of action model misconstrues inhibition of iodide uptake—a mundane biochemical event—as implicitly adverse.

Much of the problem lies in U.S. EPA's extraordinarily expansive definition of a "key event." In the ERD, the Agency defines a "key event" as "an empirically observable precursor step that is a necessary element of the mode of action or is a marker for such an element." Virtually any biological or biochemical phenomenon that is a necessary but not sufficient condition for an adverse effect could satisfy this definition. The Agency's definition obliterates any distinction among phenomena that are adverse, adaptive, or pre-adaptive. So long as it is detectable or measurable, any phenomenon could be regarded as a "key event."

1.2.2 A more sophisticated model considers fundamental biochemical and physiological phenomena.

Neurodevelopmental injury is clearly adverse and of greatest concern relative to thyroid hormone perturbation due to perchlorate exposure. Thyroid hormones are known to be important to fetal development. Critical stages of life that need to be considered are the pregnant female and her offspring. However, the magnitude of hormone changes required to affect development is not known, and reduced maternal hormone levels do not necessarily affect fetal hormone requirements.

Sustained and substantial changes in maternal T₄ are the sentinel precursor of neurodevelopmental injury. As described by Abbassi (2002), "Factors that may impair the adequacy of T₄ production by the maternal thyroid are risk factors for the developing fetus. The two well-known factors that may lead to maternal hypothyroidism are auto-immune thyroiditis and severe iodine deficiency...Iodine deficiency is only a problem when it leads to hypothyroxinemia in the mother." Inhibition of iodide uptake cannot be equated with these effects (Bruce *et al.* 2003; Lavado-Autric *et al.* 2003; Pop *et al.* 1999, 2003).

Fluctuations in triiodothyronine (T₃), T₄, and TSH are normal, adaptive phenomena and should not be construed as adverse. Physiological regulatory mechanisms protect against effects of moderate changes in iodine supply (Pisarev and Gartner 2000). Clinical and epidemiological studies show that a considerable amount of perchlorate exposure is sustained without hormone changes and humans clearly possess a significant capability to adapt to lower iodine intake without adverse effects on thyroid hormone balance. Further, inhibition of iodide uptake is such a common biochemical event that 60-70% inhibition is caused by normal dietary sources of thiocyanate (see Appendix E).

1.3 Using best scientific judgment, at what level does the chronic inhibition of iodide uptake lead to adverse, not just adaptive, health effects in humans, especially sensitive subpopulations?

Physiological regulatory mechanisms protect against effects of moderate changes in iodine supply. Clinical and epidemiological studies show that a considerable amount of perchlorate exposure is sustained without hormone changes, and humans clearly possess a significant capability to adapt to low iodine intake without adverse effects on thyroid hormone balance. Regarding perchlorate pharmacokinetics, Rothman (2002) states, "Because plasma iodide levels are very low compared to its K_m for the NIS, the perchlorate NOEL will not be changed by conceivable changes in plasma iodide or dietary intake of iodide." Evidence from human studies indicates that hormonal changes do not begin before a drinking water equivalent level exceeding 17,000 ppb (17 ppm) (Crump *et al.* 2000; Gibbs *et al.* 1998; Greer *et al.* 2002; Intertox 2003; Lamm *et al.* 1999; Lawrence *et al.* 2000; Lawrence *et al.* 2001).

In part because the inhibition of iodide uptake can be measured precisely by the radioactive iodide uptake (RAIU) test, much is known about perchlorate's mechanism of action and the quantitative dosage range separating key landmark events. Before there can be risk, several sequential events must occur:

1. *First, exposure to perchlorate must be high enough to begin inhibiting iodide uptake in the thyroid gland.* Greer et al. (2002) showed that when adult humans (men and women) consumed a dose of 0.007 mg/kg-d (equivalent to about 245 ppb in drinking water) every day for two weeks, the uptake of radioiodine by their thyroids was not significantly inhibited. At 0.02 mg/kg-d (about 700 ppb in drinking water), uptake was inhibited by approximately 18%.

Using data from other, higher doses (0.1 and 0.5 mg/kg-d) and regression analysis, Greer et al. (2002) estimated a true no effect level for inhibition of iodide uptake ranging from 0.0052 mg/kg-d to 0.0064 mg/kg-d, equivalent to a drinking water level of 180 to 220 ppb.

2. *Second, iodide uptake must be substantially inhibited to cause the thyroid gland to begin using its reserve capacity of iodide.* The exact threshold for this event is not known. Greer et al. (2002) show that perchlorate administered at a dose of 0.5 mg/kg-d (about 17,000 ppb in drinking water) for two weeks to adult volunteers causes iodide uptake to be inhibited by approximately 70%. This level of inhibition did not cause changes in serum thyroid hormone levels in men or women, or cause changes in any of the more than 15 blood chemistry values that were measured.

These data corroborate and extend those of Lawrence et al. (2000), who had shown that a mean perchlorate dose of 0.12 mg/kg-d (about 4,200 ppb in drinking water) administered to adult volunteers for two weeks inhibited radioiodine uptake by about 40% without causing changes in serum hormone levels.

3. *Third, exposure must be high enough to produce an initial change in thyroid hormone levels.* At this level, the body has an adaptive process to adjust and normalize thyroid hormones through homeostasis. It is not known how much perchlorate it takes to first trigger a change in thyroid hormone levels, but for 14 days or less the dose is greater than the amounts that have been administered in recent clinical trials in humans (Greer et al. 2002 and Lawrence et al. 2000).

The highest dose in Greer et al. (2002) mirrored the highest doses in occupational studies that also show no change in thyroid hormones. Observations in perchlorate plant workers (Gibbs et al. 1998; Lamm et al. 1999) show that perchlorate exposure at levels associated with a relatively high percentage inhibition of thyroidal iodide uptake (equivalent to up to 0.49 mg/kg-d) produce no adverse health effects. It should be of particular interest that these populations included individuals of both sexes exposed for many years (most over 5 years). In studies of long-term exposure of children to perchlorate in drinking water at concentrations as high as 120 ppb (for their entire lifespan), there were no changes in thyroid hormones observed (Crump et al. 2000).

4. *Fourth, exposure must be high enough to overcome the body's normal adaptive response to maintain thyroid hormone homeostasis.* Perchlorate can be administered in large enough doses to achieve this effect, and it has been used medicinally for this functional purpose in treating Graves' disease.

Using indirect approaches, approximate bounds can be estimated for the dose range that could cause an effect on thyroid hormones (Greer et al. 2002; Lamm et al. 2002). First,

occupational studies show *no effect* on hormone levels in workers exposed to up to 0.5 mg/kg-d (about 17,500 ppb in drinking water) for an average of up to five years. Second, the lowest dose used to control thyroid disease (either auto-immune or amiodorone-induced) reported in the literature has been 0.6 mg/kg-d (about 20,000 ppb in drinking water). Thus, the dose range of 17,500 to 20,000 ppb appears to encompass the threshold dose for thyroid hormone change due to perchlorate exposure. To achieve this effect in humans, however, it is necessary to administer perchlorate three times per day because perchlorate is quickly excreted from the body (the biological half life is 8 hours). Unlike iodide, perchlorate is not stored in the body for subsequent use.

Brabant *et al.* (1992) suggests a LOAEL for hormone changes in humans. The authors found that a dose of about 13 mg/kg-d in humans for 4 weeks caused a decrease in free thyroxine (fT₄), a decrease in intrathyroidal iodine, and a decrease in TSH, but did not deplete thyroidal iodide.

Based on findings in these studies, several scientists have concluded that if perchlorate exposure is below the threshold at which inhibition of iodide uptake could be initiated (200 ppb in drinking water), then no adverse events are possible (Goodman 2003a; Greer *et al.* 2002; Fisher 2002; Lamm *et al.* 2002).

Even 100% inhibition of iodide uptake is insufficient to ensure that substantial and sustained thyroid hormone changes will occur. To date, there have been about 40 cases (from over 20 families) of iodide transport defect related to NIS mutations (Eng and Ho 2003). Most of these have presented with goiter and hypothyroidism or compensated hypothyroidism. However, one patient with a high dietary intake of iodine who presented at age 18 with a huge goiter was euthyroid (Eng and Ho 2003). Information regarding NIS mutations has led to an understanding of alternative means for iodide to be taken up by the thyroid as supported by Wolff (1998) who states, "This genetic defect can be entirely corrected by providing large doses of iodide that enter the gland by diffusion." It is clear that lack of a functioning NIS is equivalent to 100% inhibition of iodide uptake and will generally lead to adverse effects, but not invariably. The one euthyroid patient underscores that the thyroid may still take up some iodide even with 100% inhibition of iodide uptake (see Appendix E).

1.4 Consider how the iodine-rich diet in the United States might influence the degree to which adverse effects might be expected in sensitive subpopulations.

1.4.1 *The iodine-rich diet in the United States protects everyone in the population from adverse effects resulting from environmentally relevant exposures to perchlorate.*

1.4.1.1 The U.S. population is iodine sufficient.

The World Health Organization (WHO), the United Nations International Children's Emergency Fund (UNICEF) and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) iodine classification criteria are used to evaluate and classify the adequacy of nutritional iodine levels within a population. These sources say that median urinary iodine levels of 100-199 µg/L in population studies using spot urine samples indicate "adequate/sufficient" iodine nutrition. In the U.S., use of iodized salt and consumption of iodine in bread, dairy products, and other supplements has been common since the 1920s, such that iodine deficiency goiter is virtually nonexistent. The 1988-1994 National Health and Nutrition Examination Survey (NHANES III) shows that current iodine intakes in the U.S. are considered adequate. Median urinary iodine level based on spot samples was 145 µg/L (Hollowell *et al.* 1998). Subsequently, NHANES 2000 reported a median urinary iodine level of 161 µg/L for the U.S. population. There is no evidence that an iodine deficient subpopulation exists in the U.S. and the evidence that is available strongly suggests the absence of such a population (Borak 2002; see Appendix F).

1.4.1.2 Variability of urinary iodine measurements warrants careful interpretation.

Measurement of urinary iodine concentration is regarded as "the most practical biochemical marker of iodine nutrition" when performed by appropriate methods (WHO 2001). At least four different sources of variability affect the accuracy and precision of urine iodine measurements: day-to-day variations; intra-day variations; analytical variations; and adequacy of urine collections.

Despite clear statements to the contrary by Hollowell *et al.* (1998), some recent publications have misinterpreted their NHANES III report on iodine nutrition in the U.S. (Guttikonda *et al.* 2002; Cann *et al.* 2002). These misinterpretations are probably due to misunderstanding of the imprecision of urine iodine measurements, the result of assay variability and day-to-day variations in iodine intake and iodine excretion. As a consequence, there is considerable uncertainty about urine iodine levels measured at the low extreme of a population's distribution. Moreover, because the standard colorimetric assay method is less precise at low concentrations, there is proportionately more uncertainty about low iodine concentrations. One implication of such uncertainty is that cross-sectional studies of urine iodine can be expected to find a number of individuals with very low apparent iodine levels relative to the sample population even when the sampled population has sufficient iodine intake. That was apparently the case for the NHANES III (Borak 2002; Maberly 2002).

2.0 RESPONSE TO CHARGE QUESTION II

2.1 Using best scientific judgment, what is the level where changes in thyroid hormones can lead to adverse, not just adaptive, health effects in humans, especially sensitive subpopulations?

Based on our review of the best available science, we believe that the level of perchlorate necessary to cause genuine adverse effects is extremely high when compared to environmentally relevant exposures in drinking water.

2.1.1 *Iodine sufficient pregnant women exposed to environmentally relevant doses of perchlorate are not susceptible to hypothyroxinemia and hypothyroidism due to perchlorate.*

The threshold for inhibition of iodide uptake is 10 to 40 times greater than environmentally relevant perchlorate exposures. These exposures would not be expected to cause hypothyroxinemia or hypothyroidism, either in the pregnant woman or in her developing child, because they are too low to trigger even the most elementary of precursor biochemical events. There is no reason to believe that the kinetics of substrate uptake by the NIS differ at different stages of development.

In addition, the thyroid has considerable reserve functional capacity such that an iodine sufficient pregnant woman could be denied all iodide for extended periods of time and experience no ill effect. This would not be true for a pregnant woman who, for whatever reason, has a smaller iodide reserve. But, a mere reduction in iodide uptake does not translate to an effect on the production or level of thyroid hormones. Goodman (2003a) writes, "[T]he dose-response for perchlorate inhibition of thyroidal iodine uptake should be unaffected by pregnancy, sex, or developmental stage."

2.1.2 *Babies born to women who are (or who may become) hypothyroid due to iodine deficiency are the most plausible subpopulation of concern, but even this group should be fully protected as long as chronic perchlorate exposure stays below 200 ppb in drinking water.*

Moderate to severe iodine deficiency remains the most plausible and necessary condition for low-level perchlorate exposure to pose any risk to the developing fetus. There is no reason to believe that the kinetics of substrate uptake by the NIS would differ for iodine deficient pregnant women. Moreover, there is no identifiable iodine deficient subpopulation in the U.S. In the latest NHANES, median values of urinary iodine in the U.S. population indicated adequate intake, exceeding the WHO benchmark for "iodine sufficient" populations.

2.1.3 *The level of perchlorate exposure needed to cause even transient changes in thyroid hormone levels is unknown, but there is substantial evidence from human studies that this threshold exceeds 17,000 ppb in drinking water.*

Short-term clinical studies and long-term occupational epidemiology studies demonstrate that no changes in thyroid hormones occur in healthy adults exposed to more than 17,000 ppb drinking water equivalent—750 to 1,500 times environmentally relevant exposure levels. While such levels will cause inhibition of iodide uptake, they will not result in adverse effects on thyroid function in iodine sufficient individuals. Only a sensitive subpopulation of iodine deficient individuals could face a hypothetical risk, but no such subpopulation is known to exist in the U.S.